Howard R. Sklamberg
Director
FDA/CDER/Office of Compliance

University of Georgia International GMP Conference
Athens, GA
March 2013

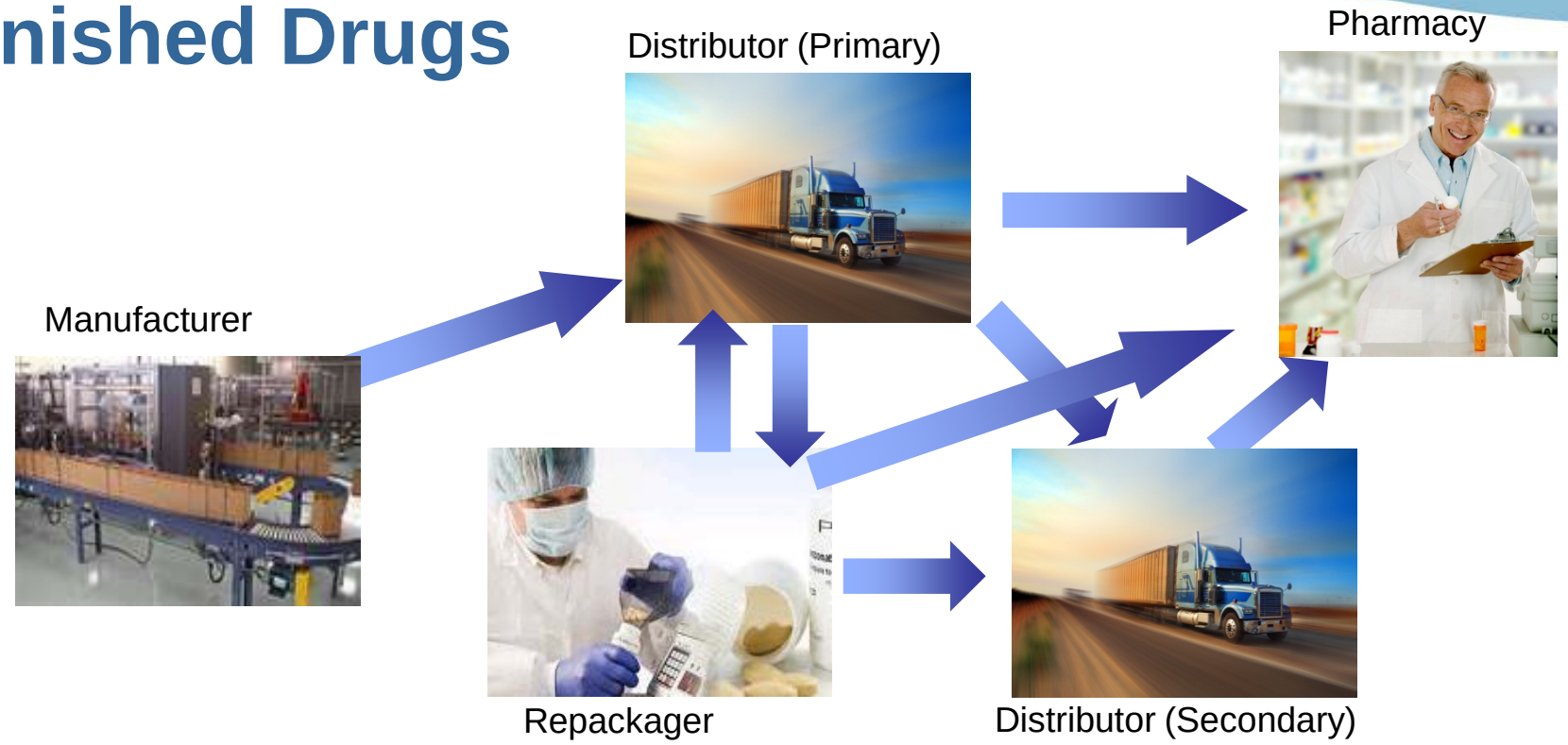
Globalization - Production

- **Drugs**
  - 80% of API manufacturers are located outside the United States
  - At least 40% of drugs on U.S. shelves come from overseas.
  - Pharmaceutical product imports increased at nearly 13% per year from 2005-2011
- **Devices**
  - Medical device imports have grown at over 10% per year from 2005-2011
  - At least 50% of all medical devices used in the United States are imported
- **Food**
  - 10-15% of all food consumed by U.S. households is imported
  - Approximately 50% of fresh fruits and 20% of fresh vegetables are imported
  - 80% of seafood eaten domestically come from outside the United States
  - Food imports have increased an average of 10% per year from 2005-2011

Challenges presented by globalization

- More dispersed facilities supplying global market
- Increasing volume of imported products
- More outsourcing of manufacturing
- Greater complexity in supply chains
- Imports coming from countries with less developed regulatory systems
- Greater opportunities for economic fraud

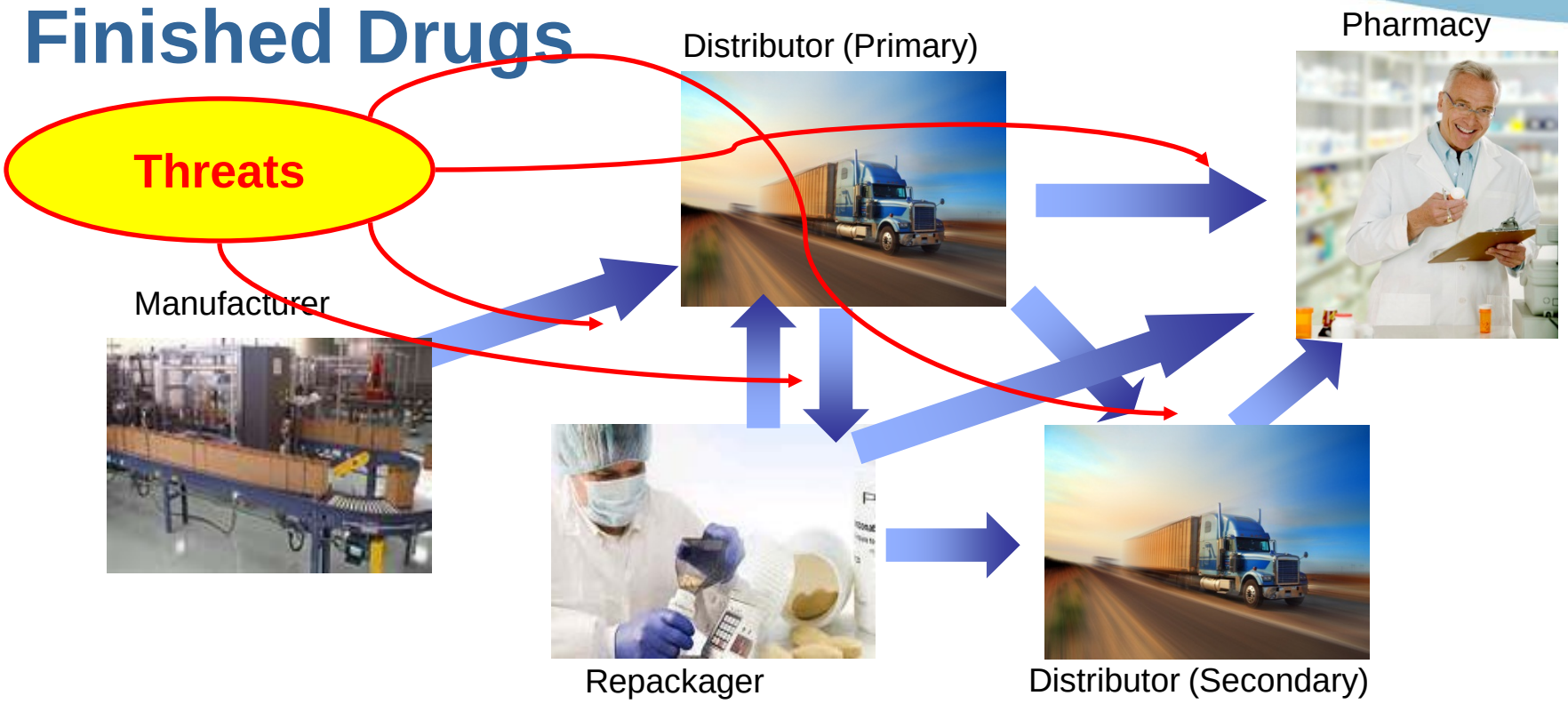
Supply Chain for Finished Drugs



Complexity of the supply chain is increased by:

- Multiple participants
- Criminal activities (diversion, theft, counterfeiting)
- Globalization of supply chains
- Rules that vary by state

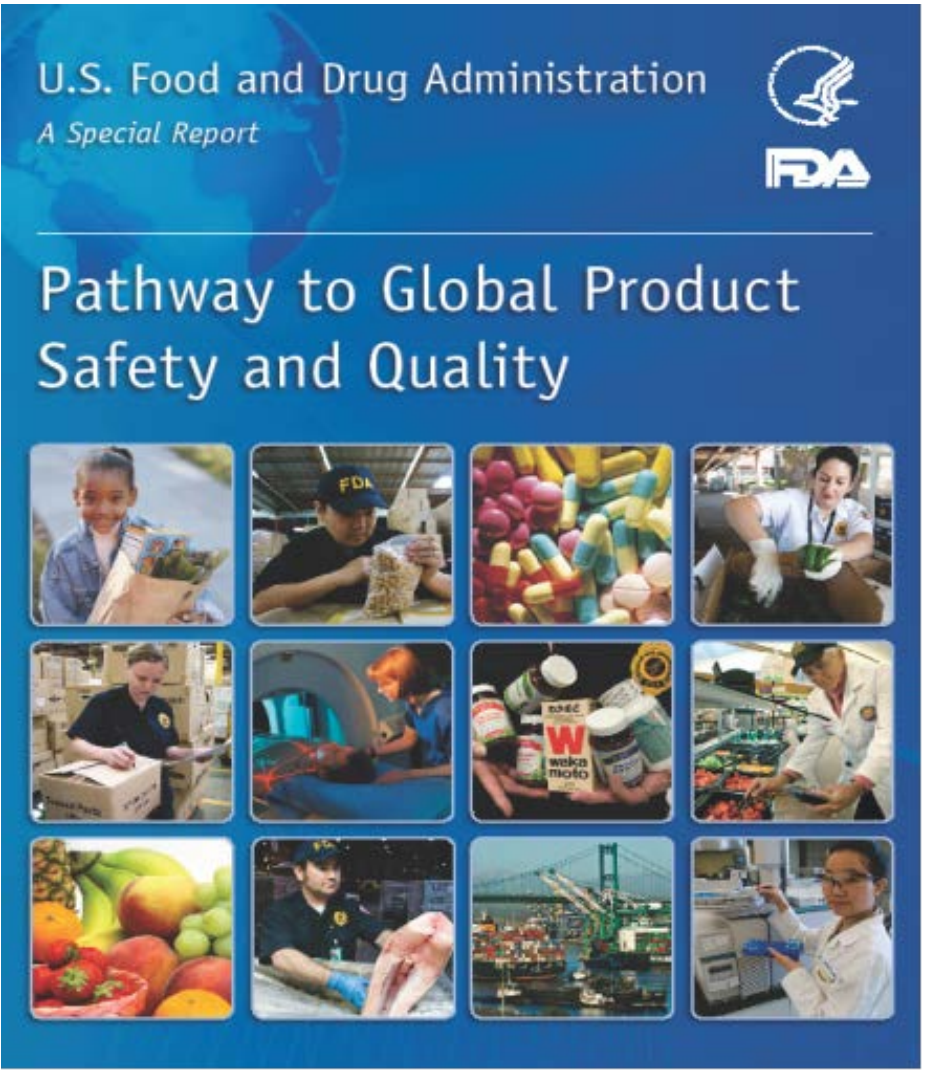
Supply Chain for Finished Drugs



Example of threats in the supply chain:

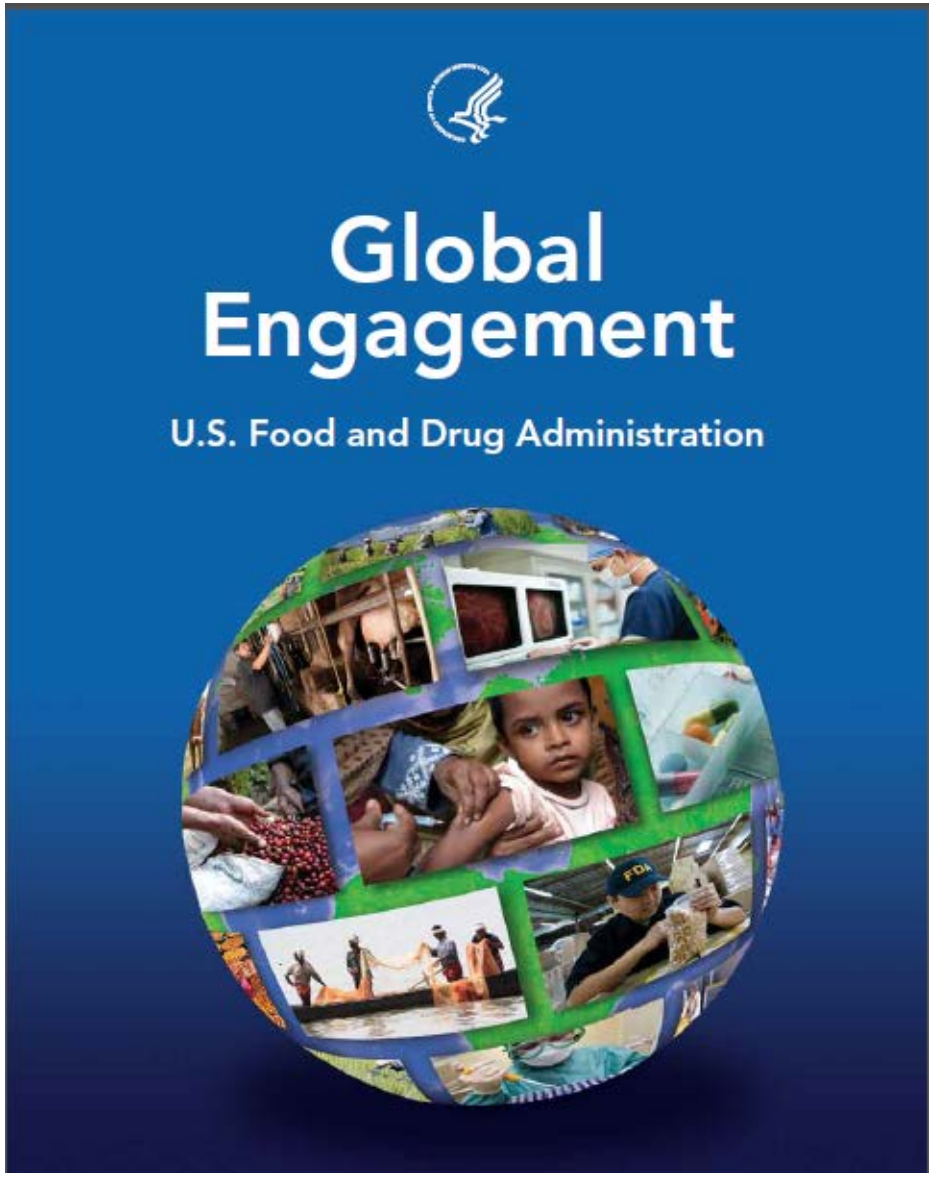
- Counterfeit/falsified drugs sold to suppliers
- Other adulterated/misbranded drugs introduced
- Stolen products reintroduced
- Diverted drugs resold

How is FDA Addressing These Challenges?



- Partner with foreign counterparts to create global coalitions of regulators focused on ensuring and improving global product safety
- Build global data-information systems and networks and proactively share data with peers
- Expand intelligence gathering, with an increased focus on risk analytics and thoroughly modernized IT capabilities
- Effectively allocate agency resources based on risk, leveraging the combined efforts of government, industry and public and private third parties

•http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofGlobalRegulatoryOperationsandPolicy/GlobalProductPathway/UCM262528.pdf

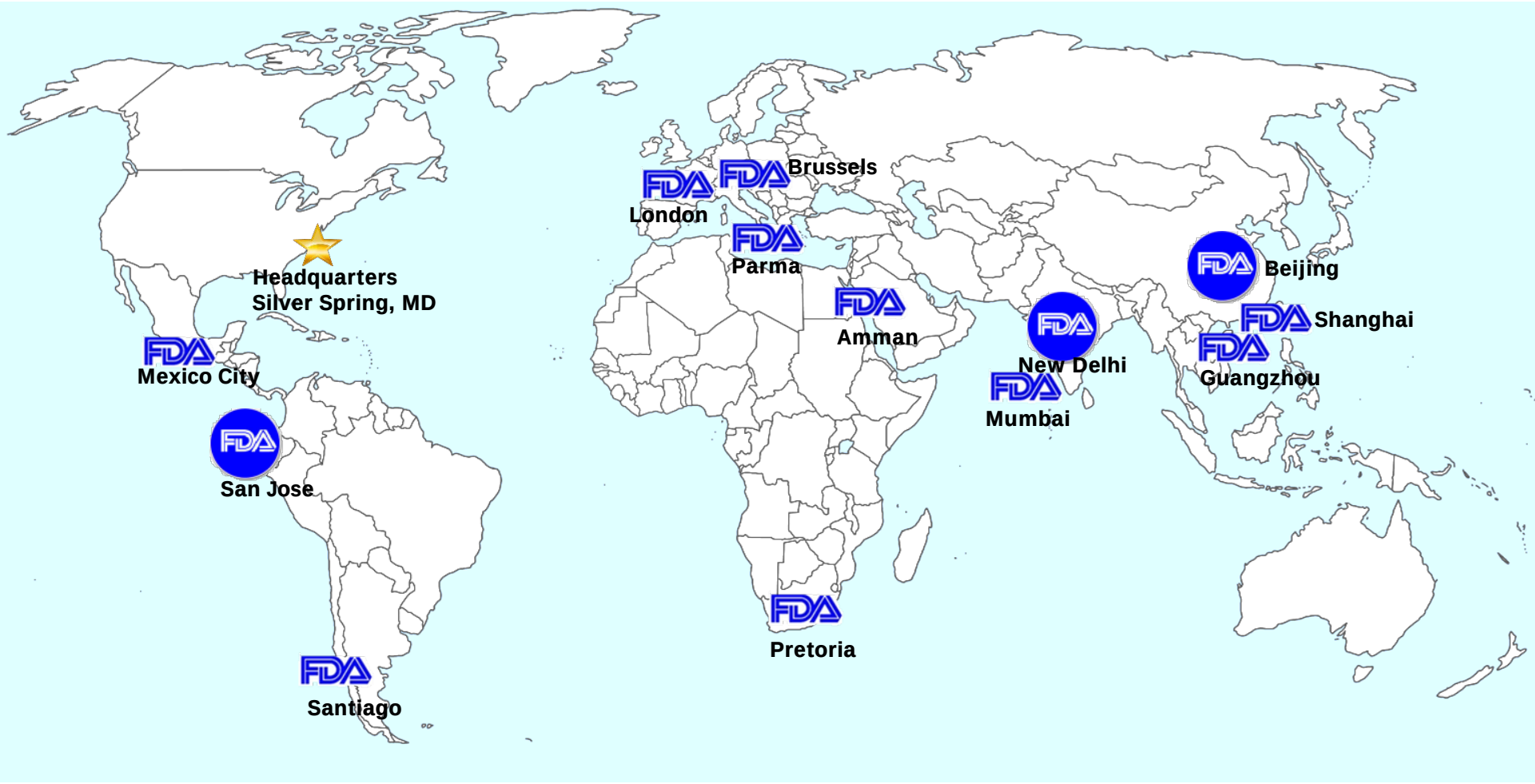


"Today we recognize that to successfully protect U.S. public health, we must think, act, and engage globally. Our interests must be broader than simply those within our own borders."

Margaret Hamburg,
FDA Commissioner

- International Offices
- Strengthening Regulatory Capacity Building
- Harmonizing Science-based Standards
- Leveraging Knowledge and Resources
- Risk-based Monitoring and Inspection
- Advancing Regulatory Science

FDA foreign offices



Global cooperation/collaboration

- U.S. government inter-agency leveraging
- Bi-lateral/multi-lateral capacity building
- World Health Organization
  - Member State Mechanism
  - Global surveillance system
- Operation Pangea V
  - INTERPOL led global operation targeting internet websites supplying illegal and dangerous drugs;
- APEC Roadmap for Global Medical Product Quality and Supply Chain Integrity
  - identify a path forward toward regulatory convergence of practices necessary to ensure the integrity of marketed medical products

Pharmaceutical Inspection Co-operation Scheme initiatives (PIC/S)

- **CDER OC initiatives with PIC/S**

  -Prior knowledge and review of revisions to EU GMP regulations and PIC/S Guidances for industry

  -Creation of common EIR Template to all PIC/S members

  -Joint Inspection Training exercises

  -Participation in “Expert Circle” groups, training, and discussions

Confidence Building to Reliance Upon

- Initiative:
  - Some GMP inspections of US and EU manufacturing sites may be deferred or waived based on inspectional findings of the other regulator.
  - FDA will exchange information as permitted under the framework of the confidentiality arrangements between EC, EMA and FDA.
  - Main objective of the initiative is to share information on inspections and GMP-related documents of common interest, and to conduct collaborative inspections when necessary.
- Benefits:
  - Reduce inspections of firms in Europe and allow FDA to shift inspection capacity to other regions
  - Provide relief to manufacturers who direct substantial resources to host inspections
  - FDA to efficiently use resources to monitor as many products as possible; wider global inspectional coverage.

Quality Focus

Commitment to quality

- Essential… from the top down and bottom up
- Cannot settle on "meeting regulators standards"
  - Must meet ***YOUR*** standards to reliably produce high quality products
- What Dr. Woodcock said…
  - proactively identify & promptly correct issues
  - design/qualify robust operations
  - maintain equipment and facilities
  - Implement robust quality management systems
- Significant impacts to the public's health
  - Cost of poor quality – $$$$$$$$$$$$
  - Cost to patients – shortages, adverse events, etc.

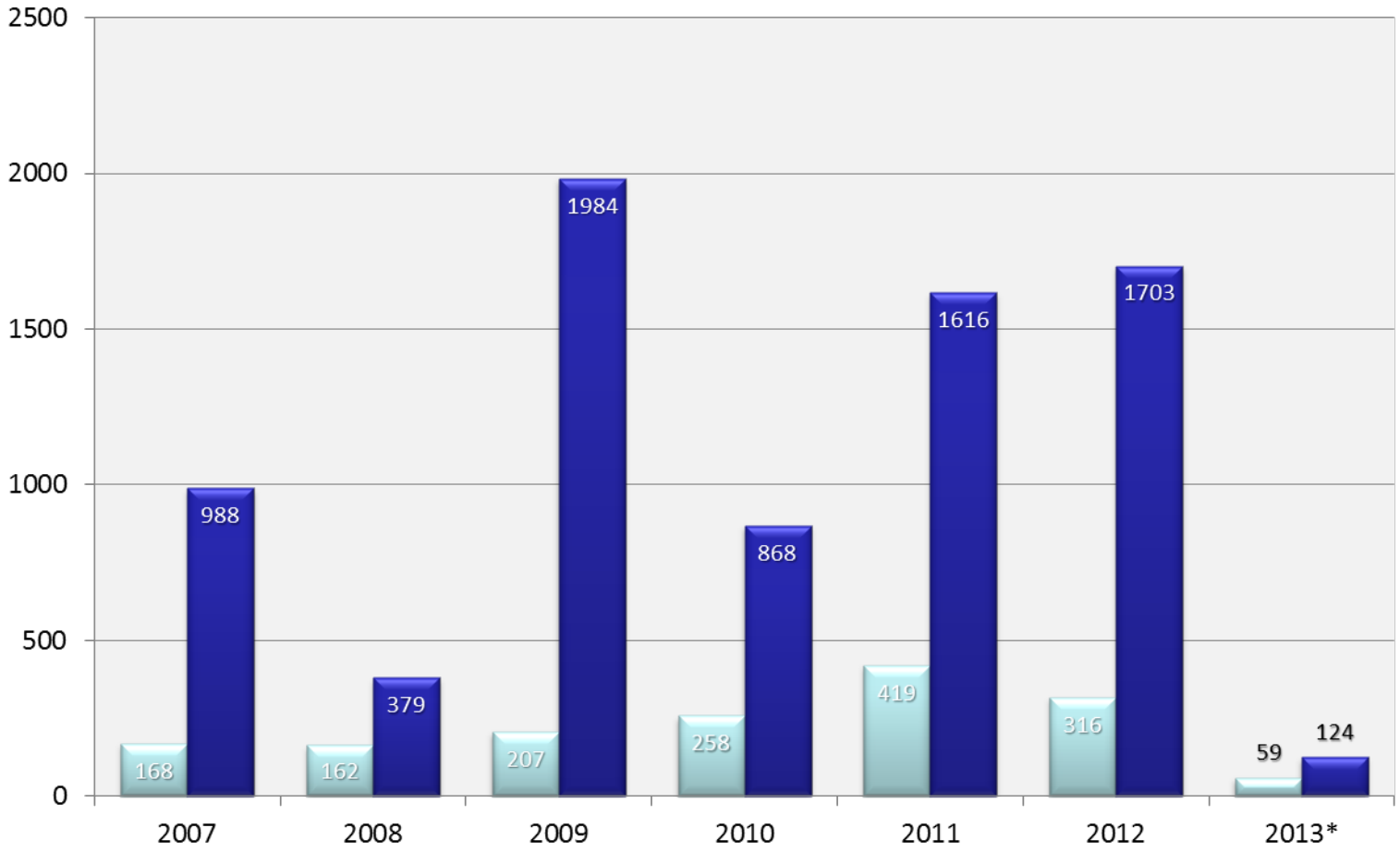
Recall definitions

- **Class I recall:** a situation in which there is a reasonable probability that the use of or exposure to a violative product will cause serious adverse health consequences or death.

- **Class II recall:** a situation in which use of or exposure to a violative product may cause temporary or medically reversible adverse health consequences or where the probability of serious adverse health consequences is remote.

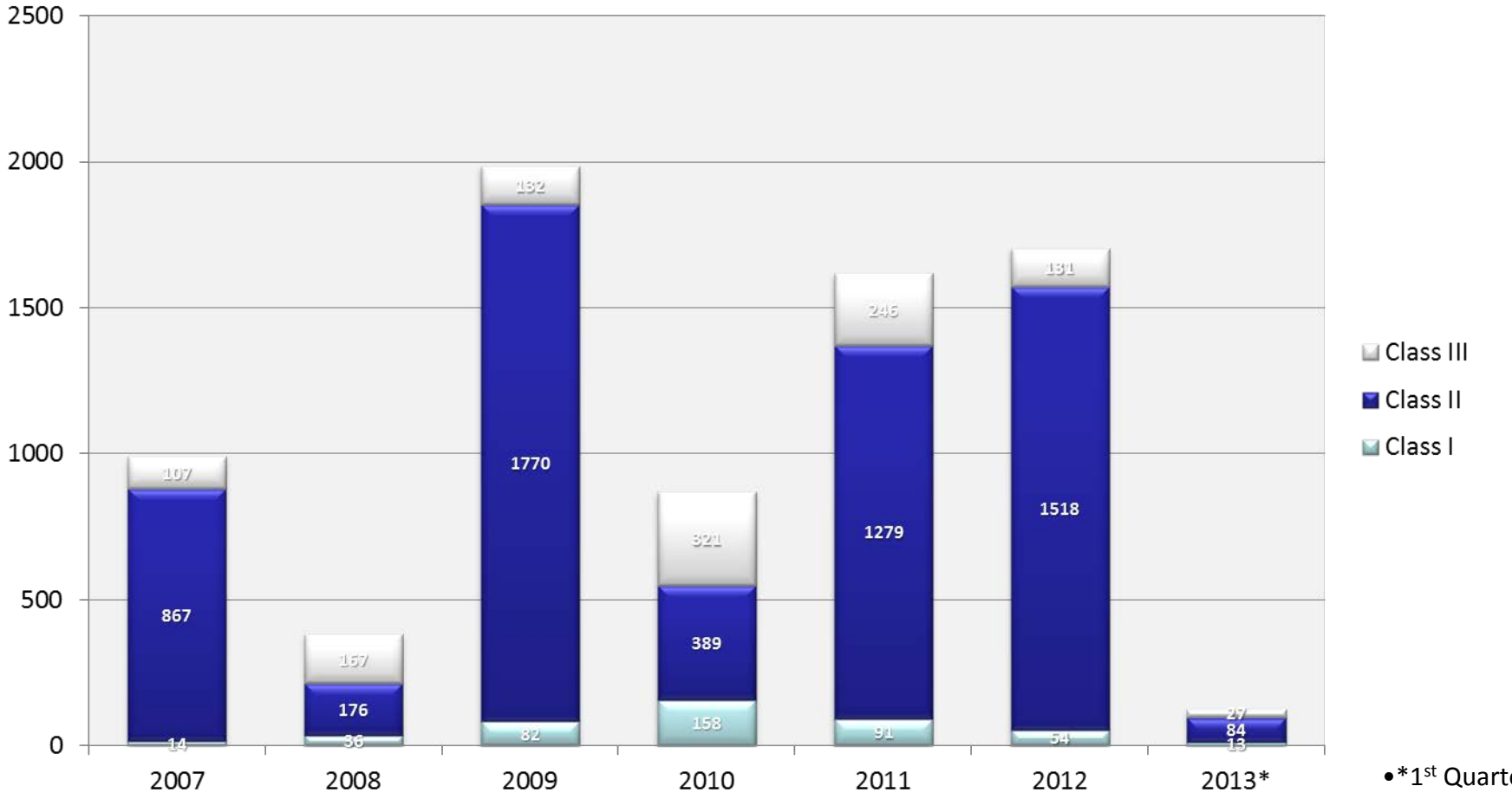
- **Class III recall:** a situation in which use of or exposure to a violative product is not likely to cause adverse health consequences

Total Event vs Product Recalls FY 07-13*



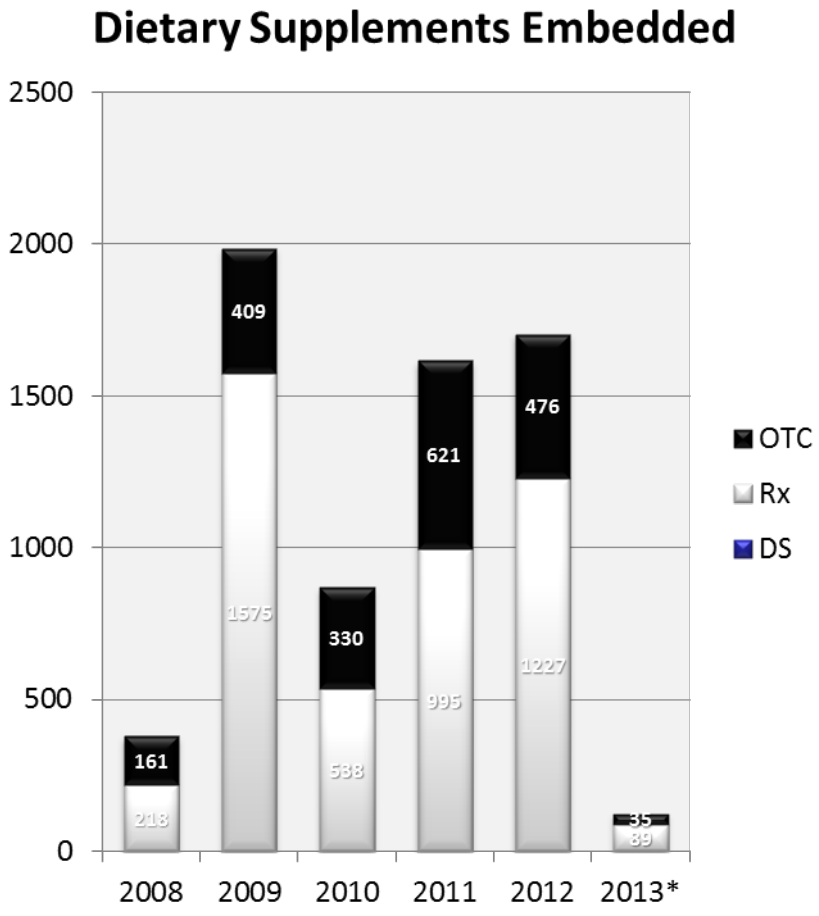
•*1st Quarter

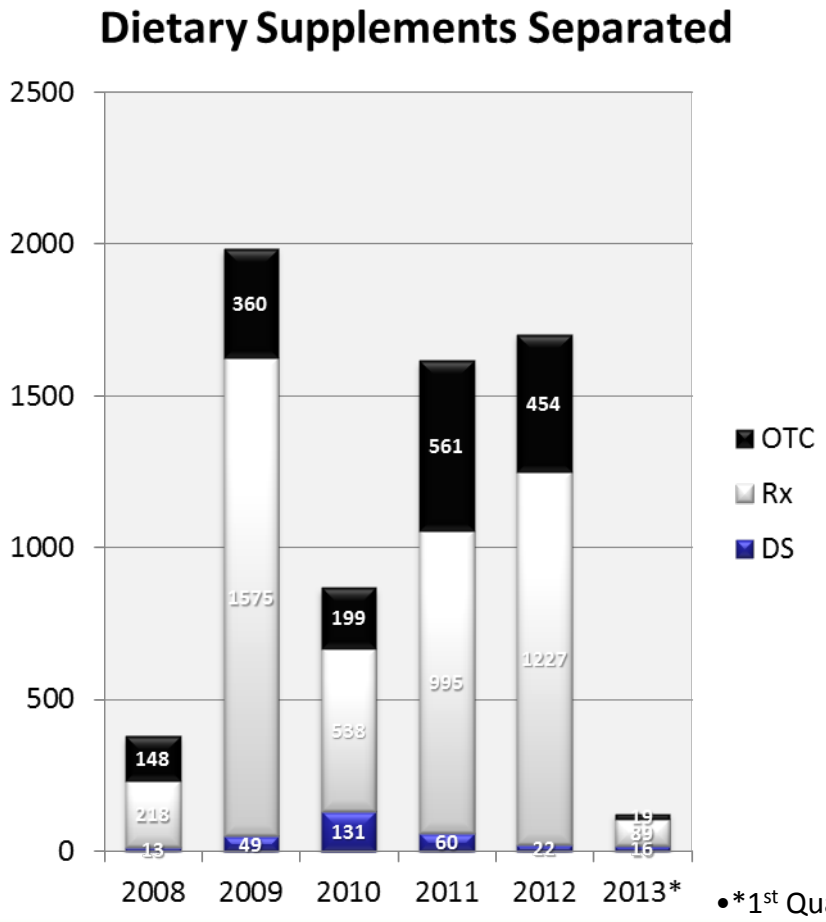
Total product recalls by class FY 07-13*



•*1st Quarter

Total product recalls by type FY 08-13*





•*1st Quarter

Major reasons for recalls FY 10-13*

2010	**Impurities Degradation Products** **GMP Deviations** **Marketed Without an Approved NDA/ANDA**
2011	**GMP Deviations** **Marketed without an Approved NDA/ANDA** **Impurities/Degradation Products**
2012	**Impurities/Degradation Products** **GMP Deviations** **Lack of Assurance of Sterility**
2013*	**Lack of Assurance of Sterility** **GMP Deviations** **Presence of Particulate Matter**

- *1st Quarter

Compounding: current law -- 503A

- Provides explicit exemption from new drug, CGMP, and adequate directions for use requirements for compounding that meets certain criteria
- Compounding that doesn't meet the criteria is considered manufacturing that is subject to all of those requirements
- Compounding requires patient specific prescription, except:
  - Allows anticipatory compounding in limited quantities before receipt of a valid prescription based on a history of the pharmacist receiving valid prescription orders for the compounded drug
- If bulk active ingredients used, must meet certain criteria
- Cannot compound:
  - Drugs withdrawn or removed from the market for safety or efficacy
  - Drugs that are essentially copies of commercially available products, regularly or in inordinate amounts
  - Drugs that are difficult to compound

Compounding: current framework

- Patchwork of State laws and regulations
  - Some states require patient specific prescriptions at all times, others may allow anticipatory compounding or office stock
  - Minority of states require compliance with USP 797
- Compounding pharmacies come in many flavors:
  - Some always get prescriptions; some do not (e.g., outsourcers); some get prescriptions for some products but not others
  - Some do sterile compounding; some do not; some do both sterile and non-sterile
  - Some compound from bulks; others do not; some do for some drugs but not all
  - Some do compounding, admixing, and repackaging; others specialize in one or another of these activities
  - Some operate in only one state; others operate in many

FDA 50-States compounding meeting

- All States represented
- Specific discussion topics regarding:
  - States ability to oversee compounding
  - Resources
  - Federal role in high risk compounding
  - Strengthening Federal/State communication
  - Role for States in enforcing a federal standard for “non-traditional” compounding
- What we heard: improve collaboration/communication; need clarity re: federal/state role; resource challenges
- Transcript/webcast of public portion of meeting on FDA website
- Docket open

Compounding path forward

- Exploring new legislation
- Current inspection activities

Drug Shortages

U.S Department of **Health & Human Services** a A A

U.S. Food and Drug Administration

Protecting and Promoting *Your* Health

A to Z Index | Follow FDA | Subscribe to Emails

SEARCH

Home | Food | Drugs | Medical Devices | Vaccines, Blood & Biologics | Animal & Veterinary | Cosmetics | Radiation-Emitting Products | Tobacco Products

Drugs

Home › Drugs › Drug Safety and Availability › Drug Shortages

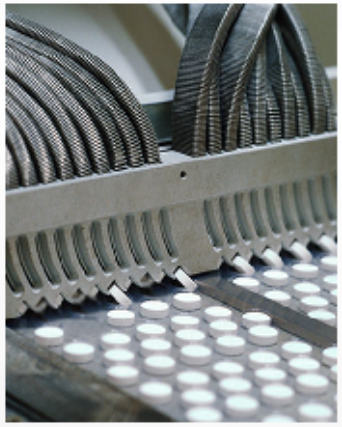
Drug Safety and Availability

- Drug Shortages
- Current Drug Shortages
- How to Report a Shortage or Supply Issue
- Resolved Drug Shortages
- Drugs to be Discontinued
- Frequently Asked Questions About Drug Shortages

Resources for You

- Drug Shortage Manual of Policies and Procedures

Drug Shortages



FDA takes great efforts, within its legal authority, to address and prevent drug shortages, which can occur for many reasons, including manufacturing and quality problems, delays, and discontinuations. The agency works closely with manufacturers of drugs in short supply to communicate the issue and to help restore availability. FDA also works with other firms who manufacturer the same drug, asking them to increase production, if possible, in order to prevent or reduce the impact of a shortage.

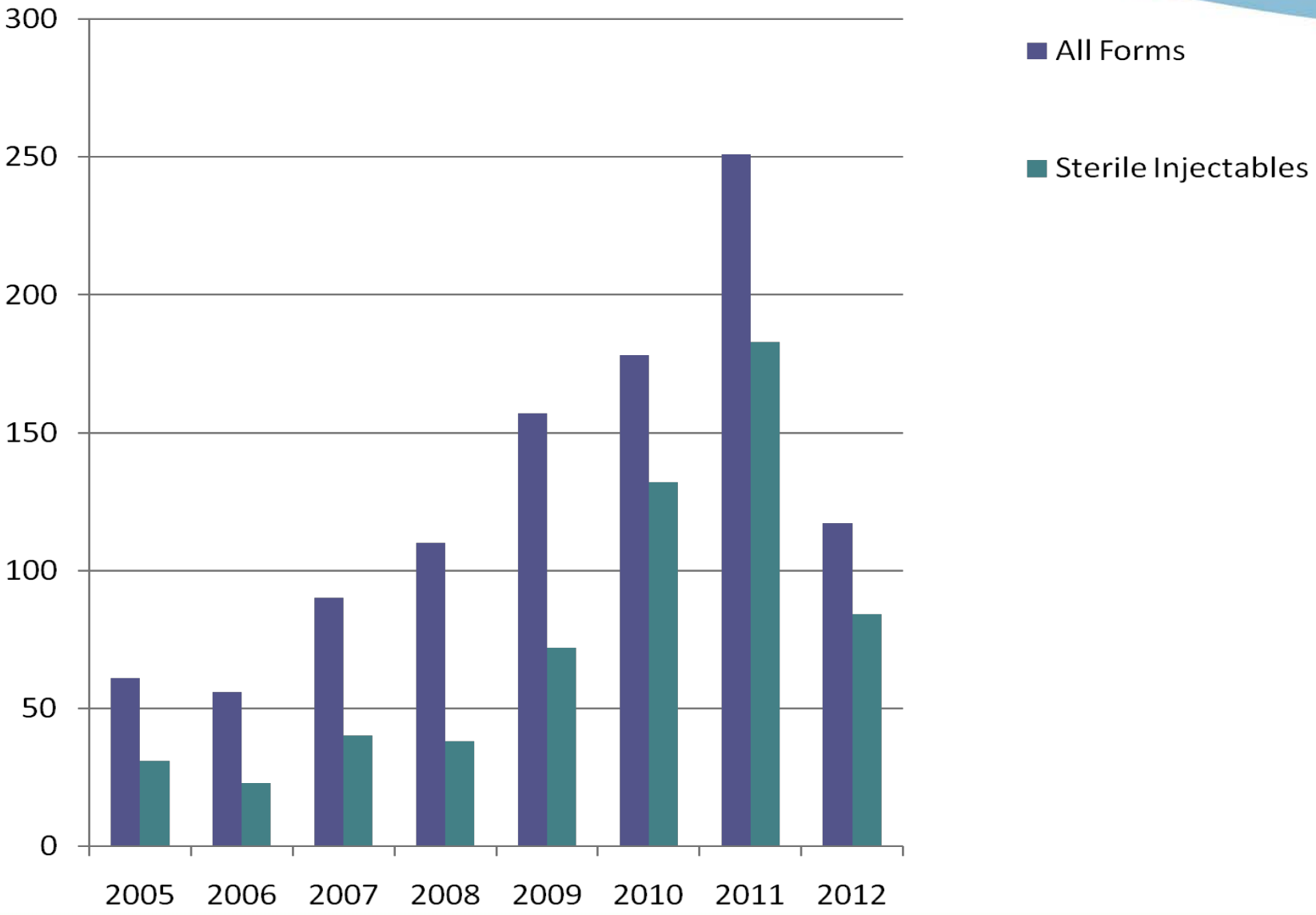
Manufacturers are not required to report information, such as reasons for shortages or the expected duration of shortages. However, many companies voluntarily provide shortage information that FDA posts on its website. FDA encourages and appreciates all reporting of shortages by manufacturers. Shortage notifications and updates may be reported to FDA at drugshortages@fda.hhs.gov.

Spotlight

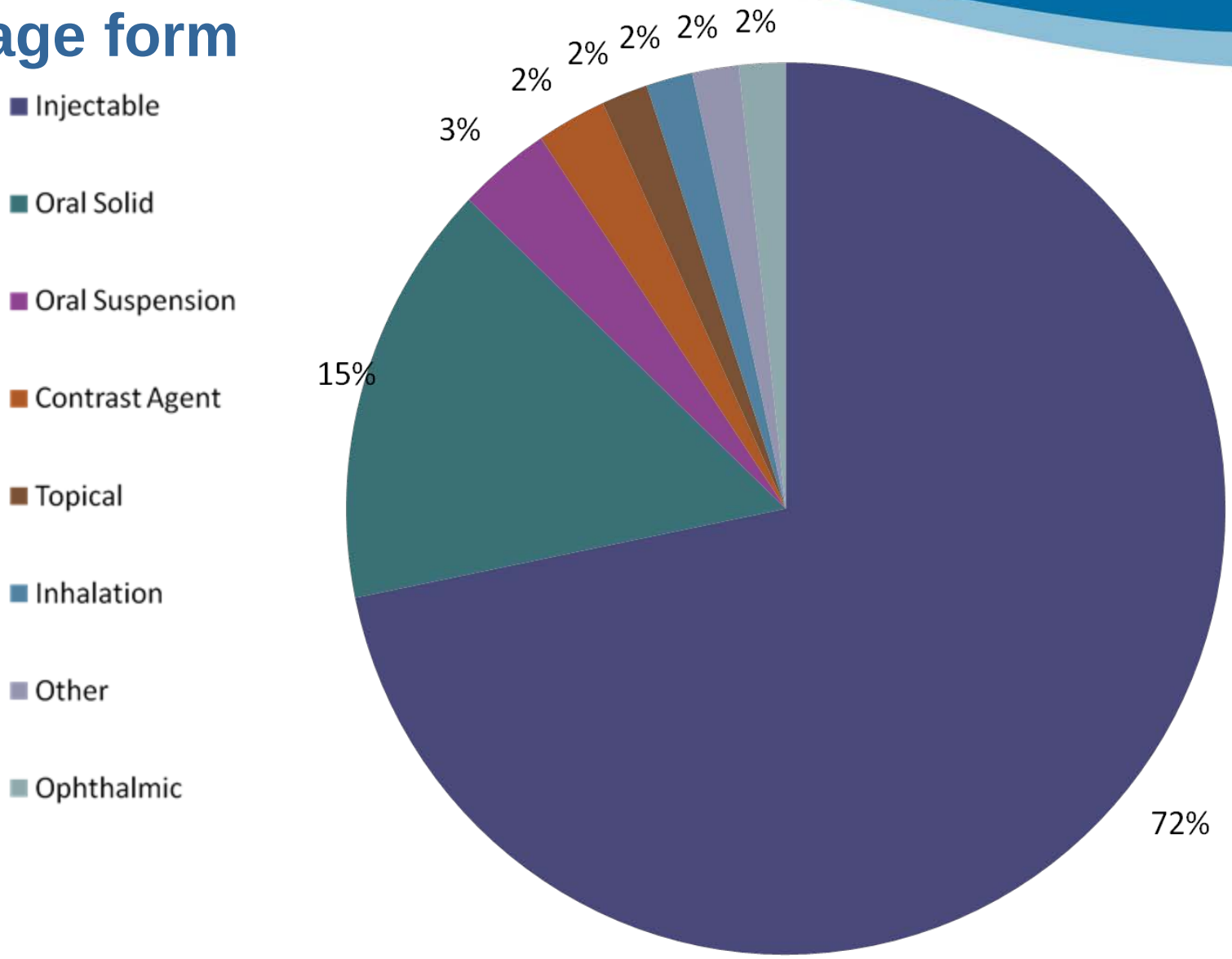
- FDA acts to bolster supply of critically needed cancer drugs
- Notification to FDA of Issues that May Result in a Prescription Drug or Biological Product Shortage (PDF - 225KB)
- Bedford Product Availability
- FDA Report: A Review of FDA's Approach to Medical Product Shortages
- Statement from FDA and HHS on Drug Shortages

http://www.fda.gov/Drugs/DrugSafety/DrugShortages/default.htm

Total US drug shortages per year



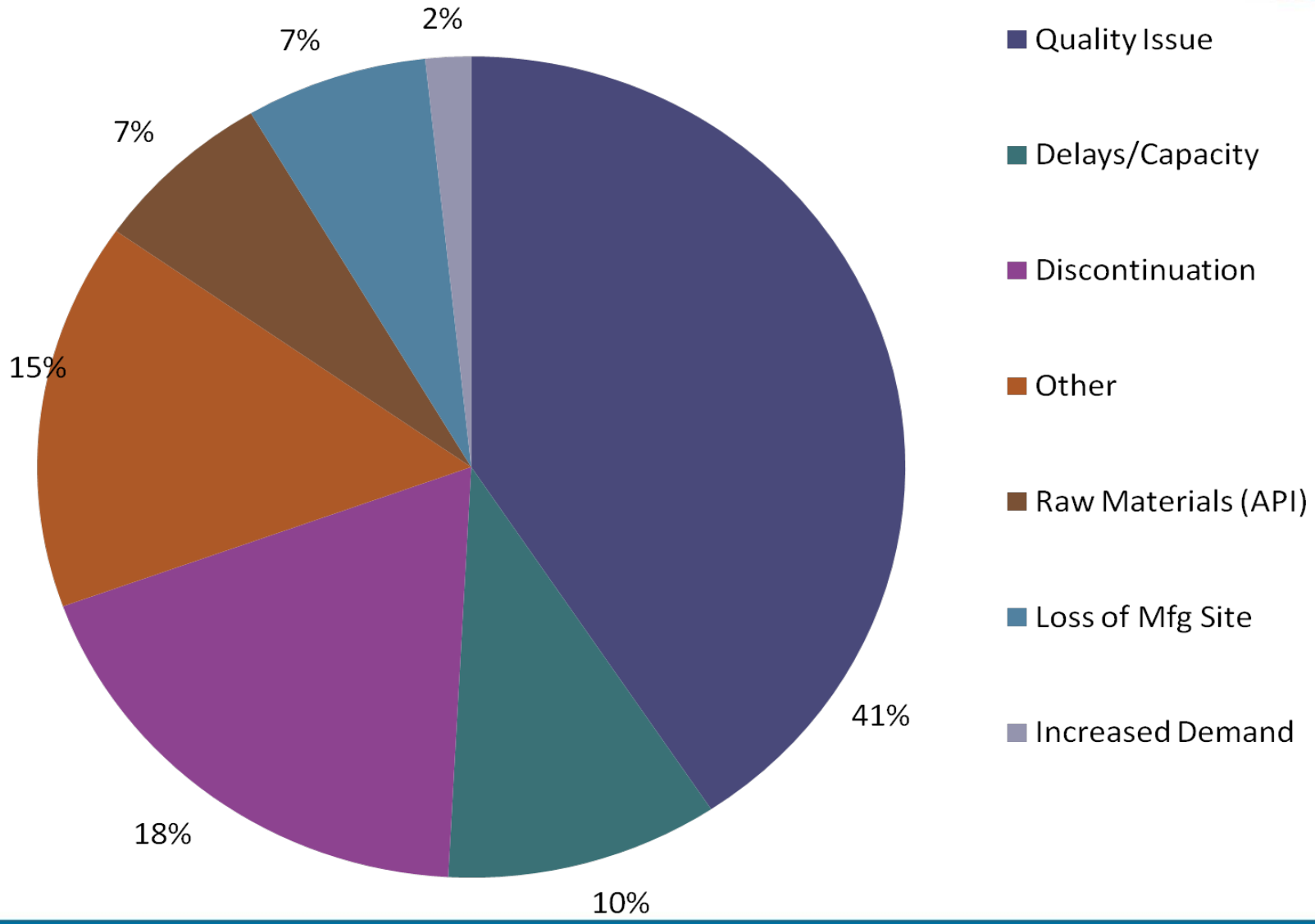
Drug shortages 2012:
By dosage form



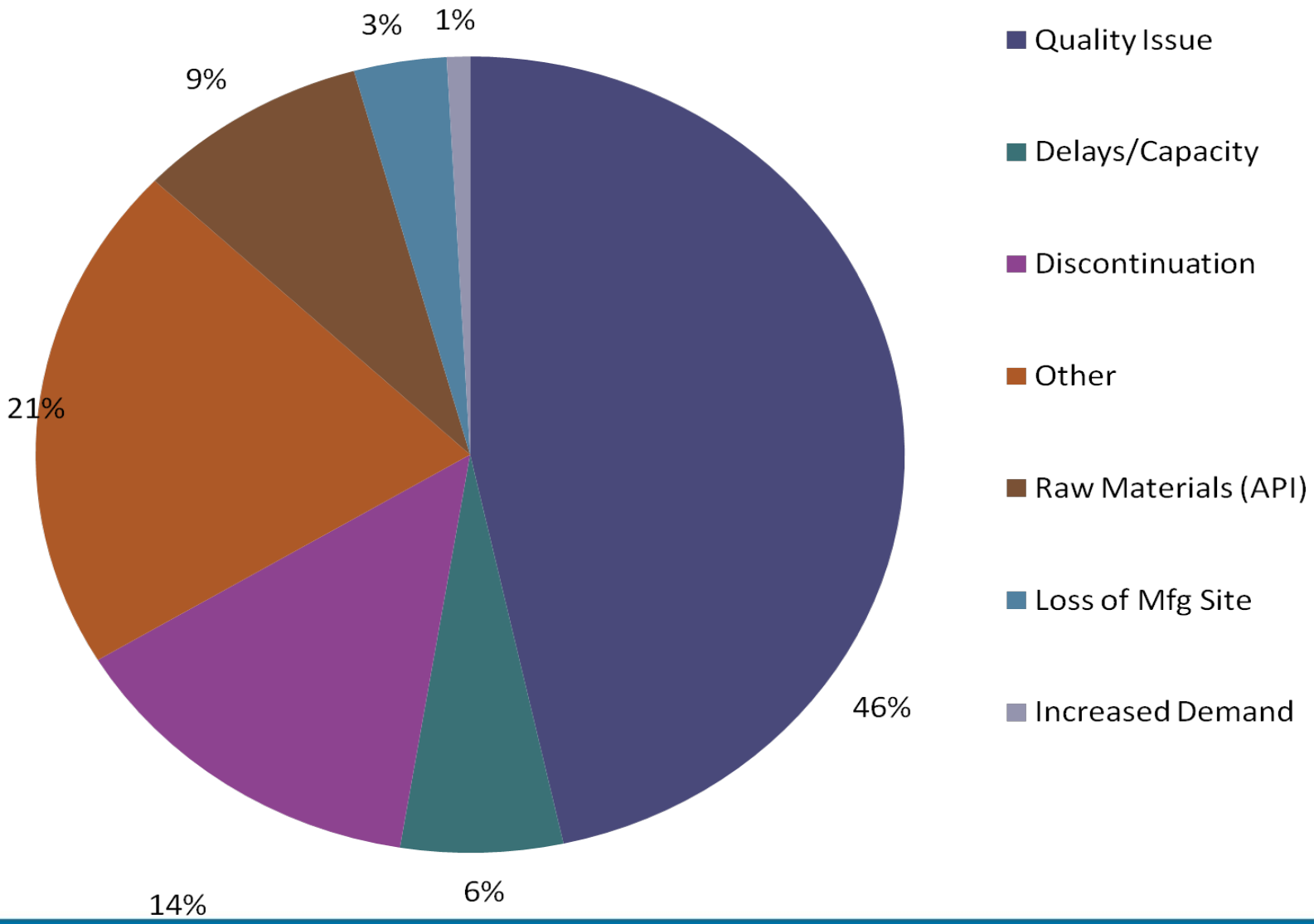
Reasons for shortages: Sterile injectables

- Failure of quality management
- State of the industry
  - Seven (7) manufacturers make up most of market
  - Contract manufacturers – firms contract out manufacturing as well as acting as contract manufacturers
- Lack of redundancy
  - Multiple products made on existing manufacturing lines
  - 24/7 production with no “cushion”
- Complex manufacturing process
  - No simple fixes
  - Problems typically affect multiple products
- Investment economics question
  - e.g., propofol 20ml sells for $0.48/vial

Reasons for sterile injectable drug shortages: 2012



Reasons for drug shortages: 2012



FDA authorities are very limited

What we can require

- Notification by sole source manufacturers*
  - Discontinuance of certain products
  - 6 months in advance or immediately if not foreseen
  - No penalty for not reporting
- Notification of manufacturing changes

What we can't require

- A company to make a drug or make more
- Notification of all production delays for all products
- How much and to whom drug is sold or distributed

FDA drug shortages program largely depends on voluntary notification by manufacturers and the public.

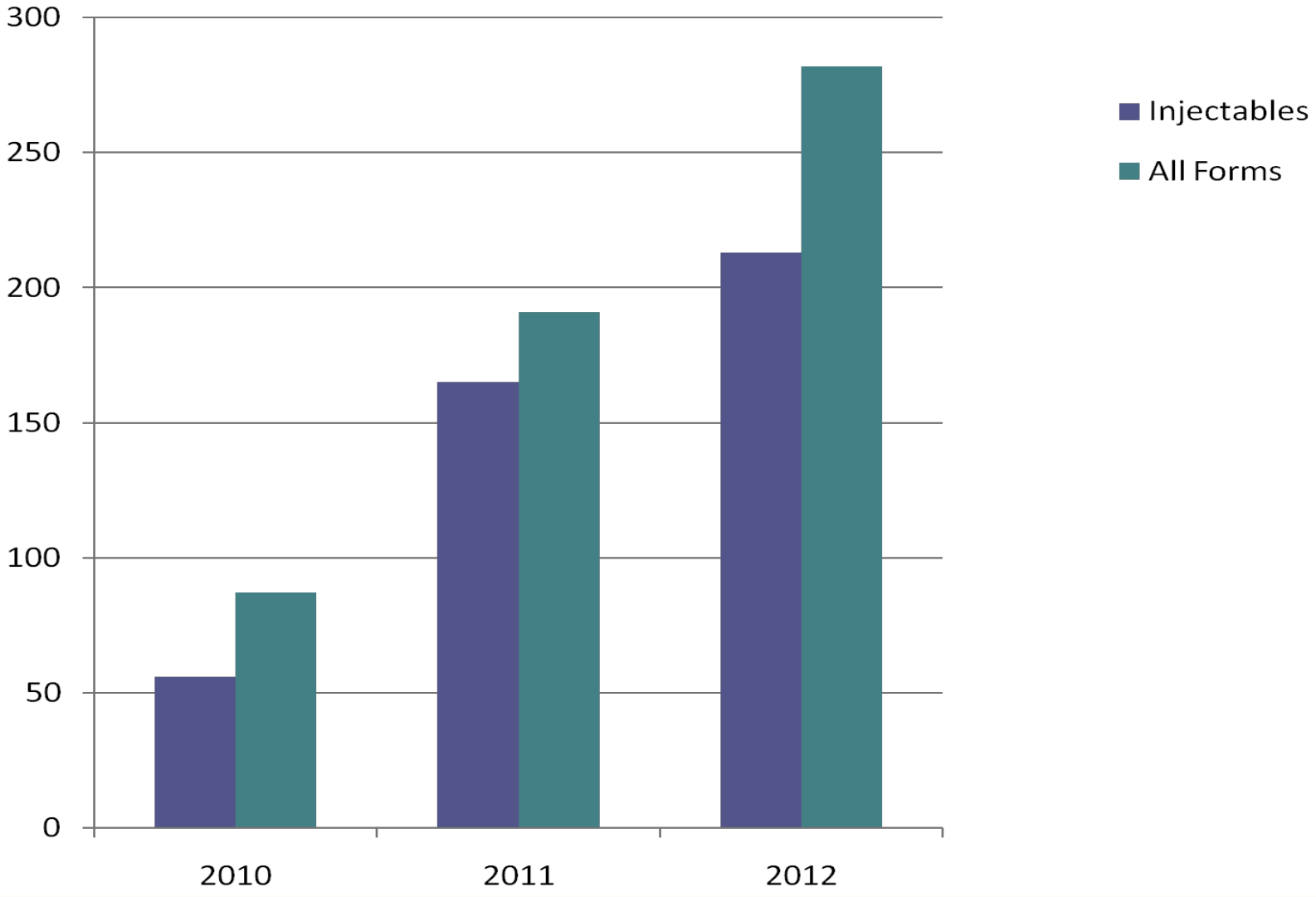
FDA's approach to prevention/mitigation

- Prioritize products that are medically necessary
- Risk/Benefit of the drug always considered
- Do everything possible to continue availability while minimizing risk to patients.
- Work with firm to address
  - We can advise, assist and expedite, but only the manufacturer can fix the problem
  - Why we encourage early notification so we are aware of problems quickly
- Be flexible and creative – and fast

FDA tool box

- Regulatory discretion: allow manufacture of medically necessary product(s) to continue
  - Minor, low risk issues usually best suited for this tool
  - In some cases require additional safety controls
    - Filters packaged with product; extra testing at plant; 3rd party oversight of production; special instructions for safe use
- Request other firms to ramp up manufacturing.
- Expedite any review of company proposals
  - New manufacture site, increased expiry, new raw material source, changes in specifications, etc.
- In rare cases, temporary importation from unapproved sources

Averted drug shortages: 2010-2012



New Legislation – FDASIA

FDASIA-User Fees

- The first 4 titles relate to user fees:
  - Gives FDA authority to collect user fees from industry
  - Steady & reliable income to bring new products to market safely & quickly
    - Prescription Drug User Fee Act **(PDUFA)**
    - Medical Device User Fee Act **(MDUFA)**
    - Generic Drug User Fee Act **(GDUFA)**
    - Biosimilar Products User Fee Act **(BsUFA)**

Title VII – Drug Supply Chain

Increased Risk Information

Registration (foreign & domestic) with UFI

Excipient information

Electronic system

Information exchange

Standards of admission for imported drugs

Registration of commercial importers

Notification

Enhanced Tools

Administrative destruction

Prohibit inspectional delay, limitation, denial, refusal

Administrative detention

Protection against intentional adulteration

Penalties for counterfeiting drugs

Extraterritorial jurisdiction

Global Supply Chain

Risk-based inspections

Records for inspection

Recognizing foreign govt. inspections

Enhancing safety and quality of drug supply / QMS

Title X: Drug Shortages

- Expedite review of applications OR inspection or re-inspection that could help mitigate or prevent a shortage OR
- Communication: prior to any enforcement action or issuance of a warning letter that could reasonably be anticipated to lead to a meaningful disruption in supply, drug shortages program shall be consulted to determine if action or letter could cause or exacerbate a shortage
- Action: if it is determined that an action or warning letter could reasonably cause or exacerbate a shortage, Secy shall evaluate the risks associated with the impact of a shortage upon patients and those risks associated with the violation before taking action, unless imminent risk of serious adverse health consequences or death to humans

What's around the corner?

- GDUFA implementation
  - ANDA backlog
  - GMP and bioequivalence inspection and compliance program ramp up
    - Includes implementation of a surveillance inspection program in parallel with the current application-based inspection model
- Enhance collaborations with foreign regulators
  - Conducting inspections- GMP, GCP, BE, PV
  - Sharing inspectional information
- Implementation of FDASIA
- Compounding pharmacies
- Continue with marketed unapproved drugs initiative
- Further secure drug supply chain

Thank You!

Howard R. Sklamberg
howard.sklamberg@fda.hhs.gov